IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Tai-Tung YIP *et al.*

Title: ***SERUM BIOMARKERS IN HEPATOCELLULAR CARCINOMA***

Appl. No.: 10/508,781

Filing Date: 9/19/2005

Examiner: Nina Archie

Art Unit: 1645

Confirmation Number: 8494

RESPONSE TO RESTRICTION REQUIREMENT

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

In response to the restriction requirement set forth in an Office Action mailed October 31, 2007, Applicant provisionally elects claims 1-7 (Group I), drawn to a method for qualifying hepatocellular carcinoma (HCC) status in a subject. Likewise with traverse, Applicant further selects for consideration protein I-M38, upon which claim 1 reads.

Examiner Archie has rationalized the restriction of Group I claims from those of Group II ("kit" claims 8-10) and Group III ("software" claims 11-14) by asserting that the special technical feature common to all three groups "is anticipated by Yang et al US Patent No. 5,702,907" (action at page 2, numbered paragraph 4). More specifically, the examiner defines the "technical feature of Group I" as "a method for qualifying hepatocellular carcinoma status in a subject," which, according to the examiner, the Yang patent teaches in terms of "analyzing a biological sample ... for a diagnostic level of a protein" (*id.*).

Applicant submits, however, that the examiner has erred in her characterization of the special technical feature, by virtue of which the three groups are actually aspects of the same invention, pursuant to PCT Rules 13.1 and 13.2. On this point, the specification expressly states that:

> *It would be highly desirable to have a biomarker or combination of biomarkers capable not only of identifying HCC but also of distinguishing it from chronic liver disease (CLD), among other conditions. The literature of HCC diagnosis has not disclosed heretofore such a biomarker or combination of biomarkers, however.*

Paragraph 0006 of the published application, US 2006/00840059. In this vein, moreover, paragraphs 0058 – 0067 of the application elaborate on the extensive data, amassed by applicant, to show that the claimed invention can distinguish HCC patients from CLD patients with a high degree of predictive success.

In sharp contrast, the Yang patent purports to describe "an oncoprotein coded for by a transforming nucleotide sequence of hepatocellular carcinomas." According to the patent, the "oncoprotein ... is an amplified gene expression product of hepatoma cells that are specifically related to hepatomas." Column 4, lines 42-44 and lines 56-58. There are no data provided that even hint at a capability to distinguish HCC patients from CLD patients. Indeed, the patent states that the described "oncoprotein and nucleic acid sequence ... can be used ... in a clinical setting [for] ... diagnosis (and/or screening) the presence and/or progress of hepatocellular carcinomas (as well as preneoplastic or pathological condition[s] of the liver)." Column 5, lines 61-67 (underscoring added).

In keeping with this indeterminate pronouncement on diagnostic efficacy, a 1990 article co-authored by Yang, in *Cancer Res. (Suppl.)* 50: 5658s – 5667s (appended), describes the 52 kD oncoprotein in question ("p52"), said to be an expression product of the "human hhc^M oncogene," with literally nothing particular about diagnostic utility. To the contrary, the paper by Yang *et al.* speculates that:

> *It would be of interest to investigate the expression of hhcM-related p52 in patients at various stages of hepatocellular carcinoma and to compare such patients' specimens with samples from individuals suffering from liver cirrhosis, as well as other nonmalignant pathological conditions of the liver, such as hepatitis B or non-a non-b virus infections.*

Page 5666s, last paragraph in right column. So far as can be determined, this "interest" never led to the further publication of p52-related data bearing on the subject of diagnostic capability.

In light of both the Yang patent itself and the contemporaneous literature illustrated by Yang *et al.* (1990), applicant submits that the Yang patent does not anticipate the special technical feature shared by the claim groupings advanced by the examiner. Accordingly, the respective claim sets of Groups I-III do relate to a single, general inventive concept and, hence, should be examined together in this application. Withdrawal of the restriction therefore is requested.

Examiner Archie also errs by requiring that applicant "choose a single protein" even while admonishing that her examination, thus constrained, "should not be construed as a species election." In addition to being flawed procedurally, this *de facto* restriction contravenes current PTO policy in relation to the process claims of Group I and their equivalent, the software (algorithm) claims of Group III, as well as to the combination ("kit") claims of Group II. Thus, "when the Markush group occurs in a claim reciting ***a process or a combination*** (not a single compound), it is sufficient [for joinder] if the members of the group are disclosed in the specification ***to possess at least one property in common which is mainly responsible for their function in the claimed relationship***, and it is clear from their very nature or from the prior art that all of them possess this property." MPEP § 2173.05(h) (emphasis added).

From the preceding discussion, it is apparent that the Markush group at issue, occurring in claims that recite a process, an algorithm or a combination, is populated by biomarker members that have a common property, which is mainly responsible for their diagnostic function in the claimed invention. Accordingly, a preclusive restriction of the claimed invention to "a single protein" violates the MPEP and should be withdrawn.

In summary, applicant requests that examination together of the three claim sets, without restriction to biomarker. Further, since the prior art on HCC diagnosis indeed suggests no biomarker or combination of biomarkers capable of distinguishing HCC from CLD, applicant submits that the present claims are patentable, and an early indication to this effect is requested.

The Commissioner is hereby authorized to charge any additional fees, which may be required under 37 CFR §§ 1.16-1.17, and to credit any overpayment to Deposit Account No. 19-0741. Should no proper payment accompany this response, then the Commissioner is authorized to charge the unpaid amount to the same deposit account. If any extensions is needed for timely acceptance of submitted papers, Applicant hereby petitions for such extension under 37 CFR §1.136 and authorizes payment of the relevant fee(s) from the deposit account.

Respectfully submitted,

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